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EXAMINER	
MYERS, CARLA J	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No. 09/582,809	Applicant(s) SEIDEL ET AL.	
	Examiner Carla Myers	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2006 and 01 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *186-220* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *186-220* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/8/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed November 1, 2006 . Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

Claims 186-220 are newly added and have been examined herein. The following Office action contains new grounds of rejection necessitated by Applicant's extensive amendments to the claims. This action is made FINAL.

Information Disclosure Statement

2. In the information disclosure statement filed in this application on November 8, 2006, the Office actions cited in the IDS do not comply with the requirements of 37 CFR § 1.98 because these Office actions are not published documents. The citations to the Office actions have been considered by the examiner, but have been lined through on the IDS since these citations are not in conformance with 37 CFR § 1.98. Additionally, the citations to Ozhin, Prokofiev, Solsberry, Wintzer and van Munster have not been considered by the examiner and have been lined through. In the response filed November 8, 2006, Applicant included a statement that Ozhin "may include disclosure relative to artificial insemination of farm animals;" Prokofiev "was cited in an application that may involve technology relevant to that of the instant application;" Solsberry "may include disclosure relative to artificial insemination of cows;" Wintzer "may include disclosure relative to artificial insemination;" and van Munster "may include disclosure relative to sex determination with interferometry." However, these vague statements of what the

documents "may" disclose do not provide a sufficient explanation of the relevance of each of the cited non-English documents. An explanation of what the documents do in fact disclose is required, as set forth in MPEP 609. Further, the citations to "Milk Production and Biosynthesis" and "Managing the Dairy Cow During the Dry Period" have not been considered and has been lined through because a publication date for this reference was not provided.

The other items of information that are otherwise in compliance with the provisions of 37 CFR §1.97-1.98 have been considered by the examiner.

The following are new grounds of rejection necessitated by Applicant's amendments to the claims:

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 186-220 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of producing bovine offspring wherein the methods comprise collecting semen from a bovine, staining the sperm cells in the semen, sorting the sperm by sex chromosomes using a MoFlo flow cytometer / cell sorter at 50 psi using 2.9% Na Citrate as a sheath fluid, collecting the sperm at approximately 500 live sperm/second into tubes containing Cornell Universal Extender (CEU) with 20% egg yolk, and using, within 5-9 hours post-sorting, 3×10^5 live, cooled

sperm to inseminate bovine that were previously synchronized with prostaglandin F-2 alpha at 12 day intervals, wherein said method results in pregnancy rates of about 80% of controls inseminated using 15.6 X 10^6 motile non-sorted/unsexed sperm (see page 25 of the specification), and while enabling for methods comprising collecting semen from a male bovine, extending the semen in homogenized milk with 7% glycerol extender plus 5% homologous seminal plasma to obtain an artificial insemination sample containing 5x 10^5 total sperm per 0.25ml straw, freezing the artificial insemination sample, thawing the sample to ambient temperature, inseminating synchronized female heifers by inserting half of the semen sample deep into the uterine horns such that 5x 10^5 total thawed sperm are used per inseminate (see page 26 of the specification), does not reasonably provide enablement for methods of producing any nonhuman mammal wherein said methods comprise obtaining an artificial insemination sample containing a low number of sperm, freezing the artificial insemination sample, thawing the artificial insemination sample, inserting any portion of the artificial insemination sample into any female nonhuman mammal, fertilizing at least one egg within said female nonhuman mammal at "success levels statistically comparable to a typical artificial insemination sample'" and producing an offspring nonhuman mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the

nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The claims are broadly drawn to for producing a nonhuman mammal comprising obtaining an artificial insemination sample containing a low number of sperm, freezing the artificial insemination sample, thawing the artificial insemination sample, inserting any portion of the artificial insemination sample into any female nonhuman mammal, fertilizing at least one egg within said female nonhuman mammal at "success levels statistically comparable to a typical artificial insemination sample'" and producing an offspring nonhuman mammal. The claims further include steps of sensing a property of the sperm cells and discriminating between sperm cells based upon a desired sex characteristic. The claims also recite using a "low number of sperm" in the insemination sample and using a portion of the insemination sample for artificial insemination. However, the claims do not define what constitutes a low number of any type of nonhuman mammalian sperm and do not state what portion of the insemination sample is used to inseminate a female nonhuman mammal (i.e., step f of "inserting a portion of said insemination sample). It is unclear as to what portion of the sample would be used in the insemination process and in view of the comprising language, it is unclear as to whether additional undefined samples may also be used for the insemination process – i.e., if multiple inseminations with different amounts of sperm may be used. The claims further include methods in which insemination occurs 12 hours after the time that is

generally regarded as optimal for a single insemination; methods in which insemination occurs up to 17 hours or later than about 10 hours after the insemination sample is established; methods in which the sperm cells are separated at a rate of at least 1200 sorts per second; and methods in which the insemination sample contains at least 60%, 70%, 80% or 90% of sperm having the desired sex characteristic (claims 172, 173, 182 and 183). The claims require the steps of freezing and then thawing the sperm and then achieving success levels "statistically comparable to a typical artificial insemination sample." The specification does not clearly set forth what constitutes statistically comparable levels of success in any type of nonhuman mammal.

The claims thereby include methods in which minimal quantities of frozen and thawed sperm are used to inseminate any nonhuman mammal and high levels of fertilization are achieved comparable to those levels obtained using "high" numbers of fresh, unsorted sperm. However, the specification has not taught one of skill in the art how to achieve such high levels of success using any type of and any number of sperm from any nonhuman mammal.

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the

specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, specification has not adequately taught one of skill in the art how to practice methods of producing any nonhuman mammal using a low number of sorted sperm and achieving success rates comparable to that obtained with a "typical insemination dosage" for the following reasons.

The claims broadly encompass methods for producing any nonhuman mammal using a low number of sperm while still achieving success rates comparable to that obtained with a typical unsorted, fresh (i.e., not frozen or thawed) insemination sample. However, the specification provides only one specific example in which such a method has been accomplished. In particular, example 1, set forth on 25 of the specification, describes a method of using a "low dose" of sex sorted sperm for artificial insemination of a bovine. The method requires collecting a sperm sample from a bovine, staining the sperm cells in the semen, sorting the sperm by sex chromosomes using a MoFlo flow cytometer / cell sorter at 50 psi using 2.9% Na Citrate as a sheath fluid, collecting the sperm at approximately 500 live sperm/second into tubes containing Cornell Universal Extender (CEU) with 20% egg yolk, cooling the sperm sample, and using 3×10^5 live, cooled sperm to inseminate bovine that were previously synchronized with prostaglandin F-2 alpha at 12 day intervals. The sorted sperm were used for insemination within 5-9 hours after sorting and the method resulted in pregnancy rates of about 80% of controls inseminated using 15.6×10^6 motile non-sorted/unsexed

sperm. It is noted that in this example, the sperm were cooled, but were not frozen and subsequently thawed.

Example 2 of the specification teaches a method for producing bovine offspring wherein the method comprises collecting sperm cells from a male bovine, extending the semen in homogenized milk with 7% glycerol extender plus 5% homologous seminal plasma to obtain an artificial insemination sample containing 2x 10^5 or 5x 10^5 total sperm per 0.25ml straw, freezing the artificial insemination sample, thawing the sample to ambient temperature, and inseminating synchronized female heifers by inserting half of the semen deep into the uterine horns 12 to 24 hours after the beginning of estrus. Seidel reports that pregnancy rates of 53%, 70% and 71% were obtained using 2x 10^5, 5x 10^5 or 10x 106 total frozen sperm/inseminate. Accordingly, the specification has enabled methods comprising each of the steps and parameters recited in Example 2 of the specification.

Example 3 of the specification also describes a method of using sex-sorted, unfrozen sperm for insemination purposes. This example states that in one instance insemination with 1-2 X10^5 sperm in .1 ml resulted in pregnancy rates of 41% at 8 weeks and in pregnancy rates of 50% at 8 weeks when insemination was performed within 10 hours of the end of sorting.

In example 4 (pages 27-28), single ovulatory heifers were inseminated with 1 or 2.5 X10^5 of sperm cooled to 5°C. Pregnancy rates were 41%, 52% and 56% for 1 Xl05, 2.5 Xl0^5 and 2.5 Xl0^6 sperm/inseminate.Thereby, insemination rates with respect to a typical dosage of unsorted sperm were 93% when 1/10^{th} the typical dosage of sperm

was used for insemination. Again, in this example, cooled sperm was employed, rather than frozen/thawed sperm.

The specification clearly sets forth the unpredictability in the art of using sex sorted sperm for artificial insemination and particularly of using low-dosages of sex sorted sperm for AI. There are an extensive number of variables which effect the viability of the sperm, the success rate of AI and the pregnancy success rate.

For example, at page 3, the specification states that "the sperm are time-critical cells. They lose their effectiveness the longer they remain unused." In Example 3, the specification teaches that when 38 heifers were inseminated about 22 hours post-sorting, none of the heifers were pregnant 8 weeks after insemination. When inseminations were done 18-29 hours post-sorting, of 33 heifers only 1 remained pregnant at 8 weeks. Additionally, when inseminations were performed 17 to 24 hours post-sorting, only 1 of 7 inseminated females was pregnant at 8 weeks. Accordingly, it is highly unpredictable as to whether sorted bovine sperm samples can be used at time periods of more than 10 or at periods of 17 or more hours post-sorting and still allow for success rates comparable to those obtained with typical inseminations. The specification also emphasizes the unpredictability of using low dosage sex sorted sperm for insemination. The specification defines "low dose" as including levels of 10% to 50% of typical, non-sorted insemination samples. However, the specification exemplifies using low dosages of sex sorted sperm only with bovine animals wherein the dosage is a minimum of 1-3 x 10^5 live, cooled sperm used within 10 hours of sorting. Given the unpredictability in using low dosages of sex sorted sperm for insemination purposes, it

is highly unpredictable as to the quantity of bovine sperm or other mammalian sperm that would acceptable to allow for fertilization success rates comparable to those obtained with high dosages of unsorted semen.

The specification (at page 27) also teaches that the handling of the sample post-sorting significantly effects the success of the insemination process. When insemination samples were shipped at ambient temperature, 0 out of 10 females became pregnant. Only when the sperm was cooled to 5C during shipping, was insemination effective.

At page 3-4, the specification discusses additional factors which prevent the hinder the use of sex-sorted sperm. It is stated that "the process through normal flow cytometer techniques may, in fact, be unacceptable for cytometric sorting of sperm cells in certain applications. The sensitivities range from dilution problems and the flow cytometers inherent need to isolate and distinguish each cell individually as well as the pressure sand other stresses which typical flow cytometry has, prior to the present invention imposed upon the cells or other substances that it was sorting. This may also represent a unique factor for sperm cells because it appears that even though the sperm cell may appear to pass through the flow cytometer and be sorted with no visually discernable side-effects, in fact, the cells themselves may have been stressed to the point that they perform less optimally in the insemination process." While this passage appears to state that these problems occurred only prior to the present invention, the specification and claims do not recite any particular advancements which allow for the ordinary artisan to overcome each of these problems when sorting sex from any organism, using any means for sensing a sex characteristic, any means for

separating the sperm, any means for collecting the sperm, any means for storing and transporting the sperm, any low dosage of sperm and any means of artificial insemination. The specification teaches that the sorting rate and pressure used to run the flow cytometer may significantly effect sperm viability. However, the majority of the claims allow for the use of any type of apparatus to sense the sex characteristic and to separate the sperm cells based on the sex characteristic. The specification does not provide sufficient guidance to enable the skilled artisan to use any apparatus under any conditions, and particularly under any conditions of pressure or sort rate, to generate insemination samples that achieve fertilization rates comparable to those obtained with unsexed, unsorted sperm cells.

The specification further teaches that the selection of a sheath fluid greatly influences the viability of the sperm cells. For instance, at page 12, the specification teaches that "the stress imposed by handling of the cells within the flow cytometer appears significant for this application...For instance, while it has been known to utilize fluids having a proper pH factor or osmoality, the present invention recognizes that there may be certain chemical compositions to which the cells may be hyper-responsive. These hyper-responsive chemical compositions may naturally vary based upon the cells or even the prior handling of the cells." The specification goes on to teach a specific citrate-based sheath fluid for sorting bovine cells and a HEPES-based sheath fluid for sorting equine cells. However, the specification does not teach chemical compositions that are suitable for sorting other types of mammalian sperm. As set forth in the specification, a sperm cells response to a chemical will vary depending on the

type of chemical, source of sperm cell and previous handling of the sperm cells. The identity of the chemicals that cause stress to sperm cells from other bovine, equine and other mammals can only be determined through experimentation. There is no predictable means for determining a priori which sheath fluids will impose minimal stress on the sperm cells and allow for the sorting of sperm cells to generate an insemination sample that can be used to fertilize eggs at the same success level as a typical insemination sample. In particular, with respect to claims 27 and 177, the specification has not enabled using any HEPES sheath fluid for the sorting of any type of sperm cell. The specification has stated that it is unexpected that HEPES-based HBGM3 solution was effective as a sheath fluid during the sorting of equine sperm. The specification has not taught that this solution can be used with other sperm cells or that other HEPES solutions can be used with equine or other types of sperm cells. In view of the unpredictable effects that chemical compositions may have on the viability of sperm cells, undue experimentation would be required to practice the methods of claims 27 and 177 as they are broadly claimed.

Other factors which influence sperm viability include different aspects of the collection process. At page 15, the specification teaches that "it may be important that the container which makes up the collector be properly sized so that it acts as some means of avoiding an impact between the cells and the container itself." The specification also discusses the criticality of selecting a proper collection fluid in order to reduce stress to the sperm cells.

The specification further teaches that the dilution process may effect the success rate of the insemination process. At page 21 of the specification, it is stated that "It has been discovered that dilution may create an effect upon the sperm cell's viability and so it may be appropriate to avoid too large a level of dilution by providing a smaller sample." However, the specification does not teach what would constitute an appropriate level of dilution or appropriate type of dilution solution for diluting the sperm of the wide array of non-bovine mammals encompassed by the claims and does not provide sufficient guidance for selecting alternative dilution levels and solutions for non-bovine sperm samples. The unpredictability surrounding the insemination process is highlighted by the passage at page 22: "The utilization of embryo transfer equipment may be used because there may be high sensitivity of the uterine wall for such low dose, sexed inseminations." Yet, the specification does not clarify which mammals require or do not require the utilization of embryo transfer equipment.

With respect to claims 205-206, the step of superovulating mammals prior to insemination is also known to effect the insemination process using low dosages of sperm. For instance, Seidel (1978. Control of Reproduction in the Cow, JR Sreenan ed., pages 268-280; cited in the IDS) teaches insemination superovulated bovine with dosages of 50 million unfrozen sperm or 60 million frozen sperm (see page 274). Seidel (page 277) reports that the previous history of the donor cows may be related to the recovery of normal of ova and thereby to the fertilization rate. Seidel (page 277) also teaches that "significantly ($p < .05$) more normal ova were recovered from donors inseminated with unfrozen than with frozen semen. Thereby, the use of unfrozen versus

frozen semen appears to be another factor which will effect the ability to use dosages of sperm of one half the typical insemination sample to inseminated superovulated bovine. Hawk (Journal Animal Sciences. 1986.63: 551- 560; cited in the IDS) teaches insemination of superovulated bovine with dosages of a total of 40 million sperm. Hawk (see abstract) teaches that the "(f)ertilization rate in first-service cows was 81% on the side of semen deposition and 68% on the opposite side (P <.01); the rates in repeat-breeders were 54% and 32% (P<.0225)." Thereby, Hawk teaches that factors such as whether the cow was previously bred and the side of insemination effect the frequency of fertilization. However, there are no specific teachings in the specification as to whether the use of repeat-breeder cows or site of insemination will effect the fertilization frequency of superovulated bovine inseminated with dosages that are one half that of the typical unsorted insemination dosage.

With respect to claim 208, the step of staining the sperm cells is also known to be critical in influencing the viability of the sperm and effectiveness of the sorting procedure to obtain viable sperm. Responsiveness to stain also varies depending on the type of stain. The specification (page 20) teaches that higher amounts of stain might "to some extent" provide better results. The specification teaches using a solution of 38uM Hoeschst 33342 stain. The specification does not specifically exemplify improved results using this concentration of stain. Claim 208 allows for the use of any stain, as long as it is present at a concentration of 38uM. However, the specification does not teach any stains other than Hoeschst 3342 that can be used at this concentration. In view of the unpredictability as to how a stain and the concentration of stain will effect the

viability of sperm cells and the sorting process, undue experimentation would be required to practice the claimed invention using any stain at a concentration of 38uM.

Additionally, the ability to apply the claimed sorting and insemination method to non-bovine mammals is highly unpredictable. The specification does not provide any specific examples of using low doses of sex sorted sperm for insemination in non-bovine animals. Given the variability in sperm viability in different species and the variability in sorting success and insemination success in different species, it is highly unpredictable as to whether the results obtained with bovine can be extended to other species. The unpredictability in applying the claimed invention to non-bovine mammals is emphasized by the teachings in the specification. At page 4, the specification states that "artificial insemination with a high success rate is one of a statistical nature in which a multitude of factors seem to interplay. Thus, solutions proposed to some degree involve a combination of factors which, when thoroughly statistically studied, will be shown to be necessary either in isolation or in combination with other factors. Such a determination is further compounded by the fact that **the results vary by species** and may be difficult to ascertain due to the fact that testing and statistical sampling on a large enough database is not likely to be worth the effort at the initial stages." Yet, the specification does not provide any specific guidance as to what particular combination of factors/conditions would be required to obtain comparable success rates in non-bovine, non-human mammals. Additionally, the teachings of Johnson (cited in the IDS; Journal of Reproduction and Fertility, 1997) highlight the unpredictability of using low dosage sex sorted sperm in other mammals. Specifically, Johnson (page 262) teaches

that "It is unlikely that the technology for small numbers of spermatozoa from cattle will be directly applied to swine because of the anatomy of the pig uterus which provides an impediment to small numbers of spermatozoa." The specification does not particularly address this limitation and does not provide any particular guidance as to how to overcome this obstacle when inseminating pigs or other mammals having a uterus of similar anatomy. Furthermore, Cran (Theriogenology, January 1997) also emphasizes the unpredictability of using low doses and/or sex sorted semen for insemination. Cran teaches that pregnancy rates of lambs were low when sex sorted semen was used for insemination. In one study, 0 of 18 ewes inseminated with low doses of X sperm lambed, while 5/12 inseminated with unsorted sperm produced lambs. In a second study, none of 5 ewes inseminated with low dose Y sperm lambed; 4/25 inseminated with low dose X sperm lambed; and 2/30 inseminated with unsorted low dose sperm lambed. Cran states that the low pregnancy rates may be due to a combination of delay between semen collection and insemination, asynchrony between insemination and ovulation, semen doe and the onset of seasonal anestrus. However, the specification and prior art do not provide any specific guidance as to how to modify the method of Cran so as to predictably generate a method in which low doses of ram semen can be used to produce fertilization rates equivalent to that obtained when using high doses of unsexed sperm. It is unpredictable as to how the methodology would need to be modified in order to effectively perform low dosage AI with sex sorted sperm in other mammals, including elephants, whales, gorillas, pandas etc. The teachings in the specification regarding bovine do not provide sufficient guidance to enable the use of

this technology in other mammals because it is unclear as to how the viability of the sperm will be effected by the rate and pressure of the sorting process, the sheath fluid used for the sorting process, the collection fluid and collection container, the dilution process, the freezing process, and the type of insemination procedure.

Accordingly, the specification emphasizes the unpredictability in the art of using low dose sex-sorted sperm for AI and teaches that a multitude of factors interact in undefined ways to influence the viability of the sorted sperm and the success rate of insemination. However, the specification teaches only one particular set of conditions – i.e., the conditions set forth in Example 1 - that were shown to be effective for achieving success rates with low dose, unfrozen sex-sorted sperm comparable to success rates achieved using a typical high dosage, nonsorted insemination sample. Sufficient guidance is not provided in the specification as to how to modify the conditions set forth in Example 1 and maintain a success rate that is about 80% of the success rate achieved with typical insemination samples. Additionally, sufficient guidance is not provided in the specification as to how to apply the methodology used with bovine to all other non-human mammals. The genus of non-human mammals is significantly large and includes a vast multitude of animals whose sperm has not been previously studied for its ability to be sorted, for its sensitivity to chemicals and the sorting process, for its sensitivity to handling and freezing processes or for its ability to be used for insemination purposes. Accordingly, extensive experimentation would be required to practice the claimed invention using other sorting and insemination conditions for bovine sperm or using sperm from non-bovine, non-human mammals.

For the reasons set forth above and in view of the high level of unpredictability in the art and the lack of specific guidance provided in the specification, undue experimentation would be required to practice the invention as it is broadly claimed.

4. Claims 186-220 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification as originally filed does not appear to provide support for newly added claims 186-220. The response filed on November 1, 2006 generally states that no new matter has been added by the amendment. However, the response fails to point to particular teachings in the specification as providing support for each of the embodiments set forth in the newly added claims.

In particular, the specification as originally filed does not appear to provide support for the broadly claimed methods of producing any type of nonhuman mammal wherein the methods comprise establishing an artificial insemination sample comprising any "low number" of sperm cells relative to any "typical artificial insemination sample," freezing said artificial insemination sample, thawing said artificial insemination sample, inserting any portion of the sample into a female nonhuman mammal, and fertilizing at least one egg within said female "at success levels statistically comparable to said typical artificial insemination sample." The disclosure in the specification of the concept of performing artificial insemination using a low dosage of sperm relative to a typical

unsorted insemination sample does not provide support for a method comprising each of the steps as set forth in claims 186-220. Further, regarding claim 189, the specification as originally filed does not appear to provide support for the amendment to recite a method in which the steps of inserting and fertilizing in a field environment comprise the steps of "repetitively inserting a significant number of said artificial insemination samples into a significant number of said females of said nonhuman mammal species in rapid succession and in farm or ranch conditions."

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 186-220 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 186-220 are indefinite over the recitation of "low number of said sperm cells relative to a typical artificial insemination sample." The term "low" is a relative term which renders the claim indefinite. The phrase "low number" is not clearly defined by the claim and the specification does not provide a standard for ascertaining the requisite number of sperm which would be considered low for any mammal. While the specification does not define the phrase "low number," the specification (page 19) states that a "low dose" is less than one-half or preferably less than about 10% of the typical number of sperm provided in a "typical artificial insemination event." However, the specification does not clearly set forth what is intended to constitute a typical artificial insemination event. The specification also states that with respect to bovine, a low dose

may be 500,000 sperm or 300,000 sperm or lower. For equine, it is stated that a low dose may be 25, 10, 5 or even one million sperm. Clearly, there is a significant degree of variability surrounding what might constitute "low number" (e.g., 25 million versus 1 million) and there is no specific teaching in the specification or art as to what is generally accepted by practioners as a "low number" with respect to bovine, equine and other members of the broadly claimed genus of nonhuman mammals. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 186-220 are indefinite over the recitation of "success levels statistically comparable to a typical artificial insemination sample." There is no fixed definition in the art for what constitutes a success level for a typical artificial insemination sample" for any nonhuman mammal and this phrase has not been clearly defined in the specification. Further, it is unclear as to what is considered to constitute "comparable levels." Accordingly, one could not determine the meets and bounds of the claimed invention.

Claim 195 is indefinite over the recitation of "after the time which is generally regarded as optimal for a single artificial insemination." This phrase is not clearly defined in the specification and there is no fixed art-recognized definition for this phrase.

Claims 199-204 and 208 are indefinite over the recitation of "establishing a cell source which supplies sperm cells to be sorted" because it is unclear as to what is intended to be encompassed by this step. The claims previously require collecting sperm cells. However, the claims do not clarify how the previously recited steps are

related to or distinct from the step of establishing a cell source which supplies sperm cells.

Claims 199-204 are indefinite over the recitation of "sensing a property of said sperm cells" because it is unclear as to what is intended to be encompassed by this phrase. It is unclear as to whether sensing encompasses actually determining a sex characteristic or whether the claims allow for guessing, estimating, inferring or predicting a sex characteristic or some other property based on some undefined attribute or characteristic. The term "sensing" does not clearly describe any particular process step for ascertaining a property of sperm and thereby one of skill in the art cannot determine what is intended to be encompassed by such a step.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103□ and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 186-189, 191-197, and 217-219 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seidel (Journal of Animal Science. July 1996, 71 (supplement 1) abstract 513 "Insemination of heifers with very low numbers of frozen spermatozoa"; cited in the IDS).

Seidel teaches methods comprising collecting semen from a male bovine, extending the semen in homogenized milk with 7% glycerol extender plus 5% homologous seminal plasma to obtain an artificial insemination sample containing 2 or $5x\ 10^5$ total sperm per 0.25ml straw, freezing the artificial insemination sample, thawing the sample to ambient temperature, inseminating synchronized female heifers by inserting half of the semen sample deep into the uterine horns and fertilizing at least one egg within said bovine. Seidel teaches that the method using $5x\ 10^5$ total frozen/thawed sperm (i.e., a "low number" of sperm) achieved fertilization success rates "statistically comparable" to that obtained using a typical insemination dosage (i.e., $10x\ 10^6$ total sperm/inseminate).

Seidel does not specifically teach that the fertilized eggs are then used to produce bovine offspring. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have produced bovine offspring from the artificially inseminated heifers in order to have provided an effective means for producing bovine offspring using low numbers of frozen spermatozoa.

Regarding claim 187, Seidel teaches applying the method to bovine.

Regarding claim 188, the specification and claims do not define the term "field environment." In the absence of any further identifying characteristics of a field

environment, the method of Seidel is considered to have been performed in a field environment.

Regarding claim 189, Seidel does not specifically teach repeating the process in a "significant number" of females in a farm or ranch condition. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have repeated the method of Seidel with additional female bovine in "farm or ranch conditions" in order to provide an effective means for inseminating female bovine under natural conditions to produce a large number of bovine offspring.

Regarding claims 191-194, Seidel teaches inserting the semen deep into each uterine horn using an embryo transfer gun (i.e., "embryo transfer equipment").

Regarding claim 195, Seidel teaches performing the artificial insemination procedure 12 hours after the onset of estrous.

Regarding claims 196 and 197, Seidel does not teach using the artificial insemination sample within 17 or 10 hours of establishing the sample. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the artificial insemination sample as soon as possible following the formation of the sample in order to have ensured the viability of the sample, thereby improving the overall effectiveness of the insemination procedure.

Regarding claim 217-219, Seidel teaches using 2 or 5x 10^5 total sperm. This is considered to be about one half or less than about 10% of sperm cells are used for insemination relative to an unstated amount of a "typical insemination sample."

7. Claims 190 is rejected under 35 U.S.C. 103(a) as being unpatentable over Seidel (July 1996) in view of Seidel (1995; cited in the IDS).

The teachings of Seidel (July 1996) are presented above. Seidel teaches insemination deep into the uterine horn ipsilateral to the ovary. Seidel does not teach insemination both ipsi and contra-lateral within the uterine horns.

However, Seidel (1995) teaches ipsilateral and contra-lateral insemination of low dose semen into females. The reference teaches that pregnancy rates were nearly identical for ipsilateral and contra-lateral insemination.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Seidel (1996) so as to have performed the insemination procedure by inserting the semen both ipsi and contra-lateral into the uterine horns because this would have provided an equally effective means for inseminating female bovine.

8. Claims 198, 202, 209, 213 and 215 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seidel (Journal of Animal Science. July 1996) in view of Seidel (Theriogenology. January 1996. vol. 45, page 309; cited in the IDS).

The teachings of Seidel (July 1996) are presented above. Seidel does not teach sorting the sperm prior to artificial insemination.

However, Seidel (Jan 1996) teaches methods for making bovine mammals comprising sorting sperm cells according to sex using flow cytometry wherein the sperm cells are sorted to purity rates of about 90%, establishing an insemination sample, inserting a low dosage (1-2 X 10^5 in .1 ml) of sorted sperm cells into the uterine horns of

the female bovine after the onset of estrus; and fertilizing the eggs of the bovine so as to produce at least one offspring of the desired sex. Seidel teaches that 11 of 22 females inseminated with sperm cooled to 5C during shipping were pregnant at 8 weeks. The sperm were deposited deep in the uterine horn ipsilateral to the ovary with the largest follicle being determined by ultrasound.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Seidel (July 1996) so as to have sex sorted the sperm as taught by Seidel (Jan 1996) prior to artificial insemination in order to have provided an effective means for controlling the sex of the bovine offspring.

Seidel (July 1996) also does not specifically teach sorting the sperm into a collector having a cushion to protect the cells from impact with the collector. However, Seidel (Jan 1996) teaches sorting the cells into an extender containing homologous seminal plasma. Collection into such a medium would have cushioned the sperm cells from impact with the collector. Accordingly, modification of the method of Seidel (July 1996) so as to have sorted the sperm cells using the method of Seidel (Jan 1996) would have resulted in a method that provided the benefit of collecting the sperm cells into a container while cushioning the sperm cells from impact with the collector.

9. Claims 204 and 214 rejected under 35 U.S.C. 103(a) as being unpatentable over Seidel (July 1996) in view of Seidel (Jan 1996) and further in view of Rens (U.S. Patent No. 5,985,216).

The teachings of Seidel are presented above. Seidel does not specify the rate of sorting and specifically does not teach sorting sperm at rates of 1200 sorts/second or operating a flow cytometer at 5-50 KHz.

Rens teaches a method of high speed flow cytometry for sorting sperm. In the method of Rens (see columns 4-6), a sample of sperm is obtained from a male mammal, the sperm is stained with Hoeschst 33342 dye in order to distinguish between viable and nonviable sperm (column 5, lines 4-10), the sperm are sorted in a high speed flow cytometer using a nozzle that forms a stable droplet containing each individual sperm cell (column 2, lines 23-32), the sperm are sorted according to their sex characteristics and isolated populations of X- and Y-chromosome bearing sperm are collected. Rens teaches sampling rates of 500 sperm/second and 2000 sperm/second (column 6). Further, the nozzle allowed for sample rates up to at least 15,000 sperm/sec (column 4, lines 29-31). Rens states that the "high level of performance is beneficial for efficient sperm sorting." Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Seidel so as to have used sorting rates of about 1200 sperm/second in order to have allowed for the faster sorting of sperm so as to have provided adequate quantities of sex-sorted samples that could be used for the insemination process.

Regarding claims 214, the combined references do not specify the size of the collection container. However, it would have been well within the skill of the art at the time the invention was made to have selected a collection container of an appropriate width in order to have prevented damaging the sperm since Rens does teach the

criticality of the dimensions of the sorting device and the orientation of the sperm within the sorting device in order to maintain sperm viability (see, for example, column 3).

10. Claims 205-207 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seidel (1996) in view of Seidel (Theriogenology (1994) 41: 168; cited in the IDS).

The teachings of Seidel (1996) and Rens are presented above. The combined references do not teach superovulating the females prior to insemination.

Seidel (1994) teaches methods for stimulating superovulation in cows. In the method of Seidel, cows are treated twice a day at 12 hour intervals with injections of 6, 6, 4, 4, 2, 2, 2, and 2 mg FSH and given three dosages of prostaglandin of 25 mg and 12.5 mg PGF-2-alpha on days 6 and 7, respectively, of FSH treatments. The superovulation treatment is initiated starting between days 9 and 14 of the estrous cycle.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Seidel so as to performed the surgical insemination procedure on females that were superovulated and synchronized using the FSH/PGF-2-alpha treatment methods as disclosed by Seidel (1994) in order to have achieved the benefit of providing a more effective and convenient means of insemination since the females could then be inseminated at the most optimal time during estrous and the timing of the insemination procedure could be scheduled to correspond with the collection and sorting of sperm.

11. Claim 203 is rejected under 35 U.S.C. 103(a) as being unpatentable over Seidel (July1996) in view of Seidel (Jan 1996) and Rens, as set forth above, and further in

view of Rath (Theriogenology (1997) 47: 75-800; cited in the IDS) and Seidel (1995; cited in the IDS).

The teachings of Seidel and Rens are presented above. The combined references do not specify the solution into which the sperm cells are collected and thereby do not teach collecting the sorted sperm in a citrate solution containing about 6% egg yolk.

However, Rath (page 796) teaches collecting sex-sorted sperm into a collection media composed of TEST extender containing 2% hen egg yolk. Thus, Rath teaches the concept of collecting sperm sorted cells into a sperm extender medium. Additionally, Seidel (1995) teaches extending sperm in Cornell Universal Extender which is known to contain citrate and egg yolk.

In view of the teachings of Rath and Seidel (1995), it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Seidel (1996) so as to have collected the sperm in an extender comprising a citrate solution and egg yolk in order to have sorted the sperm into a medium that would help to preserve the sperm and/or which could be used for subsequently freezing of the sperm. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have established a collection containing having stream matched physical characteristics in order to have provided the benefit of preserving the integrity of the sperm cells.

Maintained Rejections:

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 186-199, 201-218 and 220 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 138-145 of U.S. Patent Application No. 09/744,675. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '675 are both drawn to methods for producing a nonhuman mammal wherein the methods comprise collecting sperm cells from a male, establishing a cell source which supplies sperm cells, sorting sperm cells so as to separate the sperm cells according to sex, inserting a portion of the sperm cells into a female and fertilizing at least one egg of said female. The present claims differ from the claims of '675 in that they are limited to methods for establishing an artificial insemination sample from any nonhuman mammal, whereas the methods of '675 are broadly drawn to methods for establishing an artificial insemination sample containing sperm cells from an equine. Since equine constitute a nonhuman mammal, the species

set forth in the claims of '675 anticipates the claimed invention. Further, the present claims and the claims of '675 are both inclusive of methods in which high speed flow cytometry is used to separate sperm cells at a rate of at least 1200 sperm/s (i.e., greater than 900 sperm/s as recited in the claims of '675). The instant claims and the claims of '675 also are inclusive of methods in which the sheath fluid contains a HEPES buffered medium, methods in which a low dose of sperm cells is utilized and methods in which fertilization success rates of from 35% to 90% of that of a typical unsorted insemination dosage are achieved.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 186-220 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 124-141 of U.S. Patent Application No. 10/081,955. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '955 are both drawn to methods for producing a nonhuman mammal wherein the methods comprise collecting sperm cells from a male, establishing a cell source which supplies sperm cells, sorting sperm cells so as to separate the sperm cells according to sex, inserting a portion of the sperm cells into a female and fertilizing at least one egg of said female. The present claims differ from the claims of '955 in that they are limited to methods for establishing an artificial insemination sample from any nonhuman mammal, whereas the methods of '955 are broadly drawn to methods for establishing an artificial insemination sample containing sperm cells from an equine.

Since equine constitute a nonhuman mammal, the species set forth in the claims of '955 anticipates the claimed invention. Further, the present claims and the claims of '955 are both inclusive of methods in which high speed flow cytometry is used to separate sperm cells at a rate of at least 1200 sperm/s (i.e., greater than 900 sperm/s as recited in the claims of '955). The instant claims and the claims of '955 also are inclusive of methods in which the sheath fluid contains a HEPES buffered medium, methods in which a low dose of sperm cells is utilized and methods in which fertilization success rates of from 35% to 90% of that of a typical unsorted insemination dosage are achieved.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to arguments:

In the response, Applicants state that the amendments to the claims have overcome each of the previous grounds of rejections set forth in the prior Office action. However, for the reasons set forth above, the amendments do not overcome each of the presently applied grounds of rejection.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Carla Myers

Art Unit 1634

CARLA J. MYERS
PRIMARY EXAMINER